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     (FILE 'HOME' ENTERED AT 13:29:16 ON 23 SEP 2004)

     FILE 'BIOSIS, MEDLINE, JAPIO, EMBASE, CANCERLIT' ENTERED AT 13:29:49 ON
     23 SEP 2004
L1          35089 S (IN VIVO) AND REVIEW
L2          14196 S L1 AND DRUG?
L3           8040 S L2 AND VITRO
L4           3145 S L3 AND INHIBIT?
L5           2436 DUPLICATE REMOVE L4 (709 DUPLICATES REMOVED)
L6              2 S L5 AND BISPECIFIC?

     FILE 'STNGUIDE' ENTERED AT 13:42:18 ON 23 SEP 2004

     FILE 'EMBASE' ENTERED AT 13:49:09 ON 23 SEP 2004

     FILE 'STNGUIDE' ENTERED AT 13:49:10 ON 23 SEP 2004

     FILE 'BIOSIS, MEDLINE, JAPIO, EMBASE, CANCERLIT' ENTERED AT 13:52:57 ON
     23 SEP 2004

     FILE 'STNGUIDE' ENTERED AT 13:53:07 ON 23 SEP 2004

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expression vector
mammal cell
yeast
insect cell
human
nonhuman
clinical trial
conference paper
priority journal
Drug Descriptors:
***bispecific antibody: CT, clinical trial**
***bispecific antibody: CM, drug comparison**
***bispecific antibody: PD, pharmacology**
Fc receptor: EC, endogenous compound
tumor antigen: EC, endogenous compound
immunoglobulin G: CM, drug comparison
immunoglobulin G: PD, pharmacology
CD16 antigen: EC, endogenous compound
CD64 antigen: EC, endogenous compound
receptor subtype: EC, endogenous compound
CD89 antigen: EC, endogenous compound
antigen: EC, endogenous compound
immunoglobulin G1: CM, drug comparison
immunoglobulin G1: PK, pharmacokinetics
immunoglobulin G1: PD, pharmacology
trastuzumab: PD, pharmacology
granulocyte colony stimulating factor: PD, pharmacology
gamma interferon: PD, pharmacology
immunoglobulin F(ab) fragment: CM, drug comparison
immunoglobulin F(ab) fragment: PD, pharmacology
recombinant antibody: CT, clinical trial
recombinant antibody: CM, drug comparison
recombinant antibody: PD, pharmacology
unclassified drug

RN (immunoglobulin G) 97794-27-9; (trastuzumab) 180288-69-1; (gamma interferon) 82115-62-6

ANSWER 1 OF 2 EMBASE
on STN

AN 2002323813 EMBASE

TI **Bispecific** antibodies targeting cancer cells.

AU Peipp M.; Valerius T.

CS T. Valerius, Division of Hematology/Oncology, Department of Medicine III, University Erlangen-Nurnberg, Krankenhausstrasse 12, D-91054 Erlangen, Germany. Thomas.Valerius@med3.imed.uni-erlangen.de

SO Biochemical Society Transactions, (2002) 30/4 (507-511).
Refs: 46
ISSN: 0300-5127 CODEN: BCSTB5

CY United Kingdom

DT Journal; Conference Article

FS 016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index

LA English

SL English

AB In recent years, antibody therapy has become a new treatment modality for tumour patients, although the majority of responses are only partial and not long lasting. Based on evidence that effector-cell-mediated mechanisms significantly contribute to antibody efficacy in **vivo**, several approaches are currently persued to improve the interaction between Fc receptor-expressing effector cells and tumour target antigens. These approaches include application of Fc receptor-directed **bispecific** antibodies, which contain one specificity for a tumour-related antigen and another for a cytotoxic Fc receptor on immune effector cells. Thereby, **bispecific** antibodies selectively engage cytotoxic trigger molecules on killer cells, avoiding, for example, interaction with **inhibitory** Fc receptors. In **vitro**, chemically linked **bispecific** antibodies directed against the Fc γ receptors FcγRIII (CD16) and FcγRI (CD64), and the Fc α receptor FcαRI (CD89), were significantly more effective than conventional IgG antibodies. Recent animal studies confirmed the therapeutic potential of these constructs. However, results from clinical trials have been less promising so far and have revealed clear limitations of these molecules, such as short plasma half-lives compared with conventional antibodies. In this **review**, we briefly summarize the scientific background for **bispecific** antibodies, and describe the rationale for the generation of novel recombinant molecules. These constructs may allow us to more specifically tailor pharmacokinetic properties to the demands of clinical applications.

CT Medical Descriptors:
*cancer immunotherapy
*cancer cell
target cell
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clinical trial
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priority journal
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***bispecific antibody: PD, pharmacology**
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immunoglobulin G1: PD, pharmacology
trastuzumab: PD, pharmacology
granulocyte colony stimulating factor: PD, pharmacology
gamma interferon: PD, pharmacology
immunoglobulin F(ab) fragment: CM, drug comparison
immunoglobulin F(ab) fragment: PD, pharmacology
recombinant antibody: CT, clinical trial
recombinant antibody: CM, drug comparison
recombinant antibody: PD, pharmacology
unclassified drug

RN (immunoglobulin G) 97794-27-9; (trastuzumab) 180288-69-1; (gamma interferon) 82115-62-6

ANSWER 21 OF 62 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 10

AN 2000:170406 CAPLUS

DN 132:263753

ED Entered STN: 16 Mar 2000

TI Genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents

AU Bodey, Bela; Bodey, Bela, Jr.; Siegel, Stuart E.; Kaiser, Hans E.

CS Department of Pathology, School of Medicine, University of Southern California, Los Angeles, CA, USA

SO Current Pharmaceutical Design (2000), 6(3), 261-276
CODEN: CPDEFP; ISSN: 1381-6128

PB Bentham Science Publishers

DT Journal; General Review

LA English

CC 15-0 (Immunochemistry)
Section cross-reference(s): 1

AB A **review** with 180 refs. Classical therapeutic modalities such as surgery, radiation, and chemotherapy not only fail to cure the great majority of malignant tumors, but their employment often leads to severe and debilitating side effects. The severe cancer related morbidity is also in direct correlation with the use of x-radiation and chemotherapy, making them less than ideal forms of therapy. The development of hybridoma technol. and the advances in monoclonal antibody (MoAB) production have revitalized the initial concept of Ehrlich concerning the existence of cancer cell-targeted, specific "magic bullets". Entirely new approaches to cancer therapy that are neoplastic cell-directed, and specifically lethal to malignant cells and less toxic to normal tissues are being observed and developed, adhering to the old prayer: "Destroy the diseased tissues, preserve the normal.". Immunotherapy as a fourth modality of cancer therapy has already been developed and proven to be quite effective. Strategies for the employment of antibodies for anti-cancer immunotherapy include: Immune reaction directed destruction of cancer cells; Interference with the growth and differentiation of malignant cells; Antigen epitope directed transport of anti-cancer agents to malignant cells; Anti-idiotype vaccines; and Development of engineered (humanized) mouse monoclonals for anti-cancer therapy. In addition, a variety of different agents (e.g. toxins, radionuclides, chemotherapeutic drugs) have been conjugated to mouse and human MoABs for selective delivery to cancer cells. Preclin. observations in athymic, nude mice using xenografted human cancers and mouse, anti-human MoABs were more than impressive and have lead to the development of clin. trials. Phase I studies established the safety of employing immunoconjugates in humans, but the in **vivo therapeutic** results were less impressive. The clin. use of mouse MoABs in humans is limited due to the development of a foreign anti-globulin immune response by the human host. Genetically engineered chimeric human-mouse MoABs have been developed by replacing the mouse Fc region with the human constant region. Moreover, the framework regions of variable domains of rodent Igs were also exptl. replaced by their human equivalent These antibodies can also be designed to have specificities and effector functions determined by researchers, which may not appear in nature. The development of antibodies with two binding ends (bispecific antibodies) provided a great improvement in targeting cancer cells. The existing inadequacies of MoABs in immunotherapy may also be improved by increasing their efficiency with chemical coupling to various agents such as bacterial or plant toxins, radionuclides or cytotoxic drugs. The astonishing immunophenotypic (IP) heterogeneity of neoplastically transformed cells, the different cytotoxic activity associated with the moiety linked to given MoABs, and mostly the impressive genetic modulation capabilities of cancer cells still remain as yet unsolved difficulties in the present immunotherapy of human cancer. In writing this **review** article, one of our main goals is to encourage further clin. research with the use of genetically engineered rodent MoABs

and various immunoconjugates in the treatment of human cancer, as well as the combination of such immunotherapy with the three conventional modalities of therapy. Finally, we propose that MoAB-based immunotherapy be accepted as a conventional form of therapy and employed not only in terminal cancer patients but also, for instance, during and following surgical resection.

ST **review** immunotherapy chemotherapy anticancer monoclonal antibody

IT Drug targeting
(cancer cell specific; genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents)

IT Antitumor agents
Immunotherapy
(genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents)

IT Drug delivery systems
(immunoconjugates; genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents)

IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents)

RE.CNT 180 THERE ARE 180 CITED REFERENCES AVAILABLE FOR THIS RECORD

AN 2000271731 EMBASE

TI Emerging antibody-based HER2 (ErbB-2/neu) therapeutics.

AU Krauss W.C.; Park J.W.; Kirpotin D.B.; Hong K.; Benz C.C.

CS Dr. C.C. Benz, Division of Hematology-Oncology, University of California, Department of Medicine, 505 Parnassus Ave., San Francisco, CA 94143-1270, United States. benz@itsa.ucsf.edu

SO Breast Disease, (2000) 11/- (113-124).
Refs: 65
ISSN: 0888-6008 CODEN: BRDIE5

CY United States

DT Journal; Article

FS
016 Cancer
022 Human Genetics
030 Pharmacology
037 Drug Literature Index

LA English

SL English

AB Targeting HER2(ErbB-2/neu) overexpressing tumor cells to selectively deliver anticancer agents and thereby reduce host toxicity represents a rational and emerging strategy for the treatment of breast and other epithelial cancers. The extracellular domain of the HER2 receptor tyrosine kinase is readily accessible to systemically administered antibody-based therapeutics, including growth-**inhibiting** monclonals such as rhuMAbHER2 (trastuzmab/Herceptin(C)) as well as anti-HER2 immunotoxins, antibody-dependent enzyme prodrug therapy (ADEPT), and immune cell recruiting **bispecific** antibodies. In addition to summarizing recent advances in these antibody-based strategies, this **review** focuses on preclinical advances in the development of anti-HER2 immunoliposomes (ILs) as a platform technology for targeted **drug** delivery. Extensive in **vitro** and in **vivo** testing including efficacy and tumor uptake studies in multiple human tumor xenograft models now provide conclusive evidence for the superior therapeutic efficacy of anti-HER2 ILs-doxorubicin (dox) over free dox or liposomal (Ls)-dox, and even over combinations of dox and Ls-dox with rhuMAbHER2. As anti-HER2 ILs-dox approaches clinical testing in patients with advanced HER2 overexpressing breast cancer, future applications of this novel targeting strategy will also broaden to include intracellular delivery of other anticancer agents as well as therapeutic nucleic acids (oligonucleotides, genes).

CT Medical Descriptors:

Search results
LCook 9/23/04

ANSWER 1 OF 2 EMBASE
on STN

AN 2002323813 EMBASE

TI **Bispecific** antibodies targeting cancer cells.

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*cancer immunotherapy
*cancer cell
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  drug mechanism
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  in vivo study
protein protein interaction
cell activation
killer cell
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  in vitro study
plasma half life
antibody structure
antibody engineering
antibody production
protein expression

ANSWER 58 OF 62 CANCERLIT on STN
AN 87627956 CANCERLIT
DN 87627956
TI ANTIBODY TARGETING OF ANTI-CANCER AGENTS.
AU Embleton M J; Garnett M C
CS Cancer Research Campaign Laboratories, Univ. of Nottingham, Nottingham, England.
SO Non-serial, (1985) Monoclonal Antibodies for Cancer Detection and Therapy. Baldwin RW, Byers VS, eds. Orlando, Florida, Academic Press, p. 317-44, 1985. .
DT Book; (MONOGRAPH)
LA English
FS Institute for Cell and Developmental Biology
EM 198701
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB Experience in drug targeting using a monoclonal antibody designated 791T/36, which was raised against a cultured human osteogenic sarcoma cell line, is **reviewed** under the following headings: design of conjugates (choice of antibody, choice of cytotoxic agents, advantages and disadvantages of carriers, preparation of conjugates); in vitro properties of conjugates (retention of antibody-binding activity, in vitro cytotoxicity); mode of action of MTX (methotrexate)-HSA (human serum albumin)-791T/36 conjugates (general principles of cytotoxicity for targeted drugs, specificity of action, lysosomotropic action of conjugate, intracellular transport of MTX); and in vivo aspects of MTX-HSA-791T/36 (general principles, in **vivo therapeutic** activity of MTX-HSA-791T/36 conjugates). Experience discussed is based on a model system in which the target cells constitute a relatively homogeneous population in terms of antigen expression and drug sensitivity. This characteristic is unlikely to be shared by primary and metastatic tumors in human patients. Criteria need to be established for the choice of antibody vectors. The main criteria have been considered and one of these, specificity, may be checked by careful immunohistological studies using sections of normal or neoplastic tissues, and by observing the ability of radiolabeled antibody to localize at the tumor site. It is possible to link therapeutic quantities of a conventional cytotoxic drug to a monoclonal antibody, which then confers upon the drug selectivity of action preferentially against target cells expressing a defined antigen. The aim of targeted therapy is to produce conjugates less toxic than the free drug, while retaining significant antitumor properties. Present progress suggests that the approach taken offers considerable potential for the future. (46 Refs)
RN 59-05-2 (Methotrexate)
CN 0 (methotrexate-serum albumin); 0 (Antibodies, Monoclonal); 0 (Antineoplastic Agents); 0 (Binding Sites, Antibody); 0 (Serum Albumin)

ANSWER 58 OF 62 CANCERLIT on STN
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ANSWER 54 OF 62 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1989:45 CAPLUS
DN 110:45
ED Entered STN: 06 Jan 1989
TI Immunotoxins for in **vivo therapy**: where are we?
AU Neville, David M., Jr.
CS Lab. Mol. Biol., Natl. Inst. Ment. Health, Bethesda, MD, 20894, USA
SO Annals of the New York Academy of Sciences (1987), 507(Biol. Approaches Controlled Delivery Drugs), 155-64
CODEN: ANYAA9; ISSN: 0077-8923
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A **review** with 34 refs.
ST **review** immunotoxin therapy
IT Neoplasm inhibitors
(immunotoxins as)
IT Toxins
RL: BIOL (Biological study)
(immuno-, therapy with)

ANSWER 54 OF 62 CAPLUS COPYRIGHT 2004 ACS on STN

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RL: BIOL (Biological study)
(immuno-, therapy with)

ANSWER 34 OF 62 EMBASE
on STN

AN 96251000 EMBASE

DN 1996251000

TI The biotechnology of gene therapy.

AU Pappas M.G.

CS Advanced Instruments, Inc., Two Technology Way,Norwood, MA 02062, United States

SO Drug Development and Industrial Pharmacy, (1996) 22/8 (791-803).
ISSN: 0363-9045 CODEN: DDIPD8

CY United States

DT Journal; General Review

FS 004 Microbiology
005 General Pathology and Pathological Anatomy
016 Cancer
022 Human Genetics
029 Clinical Biochemistry

LA English

SL English

AB The prospect for correcting highly morbid or fatal inherited diseases, or ameliorating cancer and acquired, deadly infectious diseases such as AIDS using gene therapy is very exciting. Numerous recent advances in molecular biology make it possible, not only to identify and locate genes associated with human inherited disorders and cancers, but to potentially correct these disorders with functional genes. These advances include more rapid gene identification, isolation and sequencing techniques, a better understanding of the functions and relationships between genes and their products in vivo, the development and study of human and model organism genomes, elucidation of genetic disease pathology using animal genetic disease models, advanced computer amino acid and nucleotide sequencing software and data bases, and the development and use of novel chemical, physical, and viral vector gene delivery methods. Functional genes are introduced using two approaches, ex vivo and in vivo gene therapy. In ex **vivo therapy**, autologous cells are removed from the patient, genetically altered by inserting the functional gene, characterized, and then returned to the patient; in in **vivo therapy**, functional genes are packaged for delivery directly into the patient, where cellular uptake and gene expression occurs. Scores of clinical trials have been federally approved to treat patients with a variety of inherited disorders, cancers, and acquired diseases using these two approaches. Roadblocks to long-lasting gene therapy include understanding more completely the biological functions of somatic cells or organs targeted for gene therapy, targeting appropriate host cells and achieving high gene delivery rates in these cells, regulating and sustaining gene expression through optimal DNA insertion into chromosomes such that other cellular functions are not adversely affected, and the prevention of vector-induced diseases or cancers. Ethical considerations regarding proper use of somatic gene therapy and the potential for germline gene therapy must also be seriously considered. The prospect of permanent correction of highly morbid or fatal maladies using gene therapy could prove to be one of the great advances in public health and could revolutionize the identification and gene-drug treatment of a broad spectrum of inherited and acquired human diseases.

CT Medical Descriptors:
*gene targeting
*gene therapy
*genetic disorder: ET, etiology
animal model
ethics
gene expression
gene sequence
genetic analysis

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genetic analysis

genetic engineering
human
nonhuman
  review

genetic engineering
human
nonhuman
  review

genetic engineering
human
nonhuman
review

ANSWER 22 OF 62 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:3109 CAPLUS
DN 132:259965
ED Entered STN: 03 Jan 2000
TI Fas ligand: a potential target for therapeutic induction of apoptosis and enhancing immunotherapy in cancer
AU O'Connell, Joe
CS Department of Medicine, University Hospital, Cork, Ire.
SO Emerging Therapeutic Targets (1999), 3(4), 601-611
CODEN: ETTAF7; ISSN: 1460-0412
PB Ashley Publications
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
Section cross-reference(s): 15
AB A **review** with 98 refs. Fas (CD95/APO-1) is a cell surface receptor which mediates a potent apoptotic death signal upon engagement by its ligand, FasL. Since tumor cells frequently co-express Fas and FasL, the prospect of therapeutically stimulating autocrine suicide of cancer cells via the Fas pathway is tantalizing. To achieve this, mechanisms of acquired resistance to Fas-mediated apoptosis, inherent in cancers, must be overcome. Indeed, expression of FasL by Fas-resistant tumors appears to enhance malignancy by triggering apoptosis of Fas-sensitive antitumor immune effector cells. Therapeutic inhibition of this 'Fas counterattack' against antitumor immune responses might improve immunotherapeutic approaches. Although restoring the Fas-sensitivity of tumors and inhibiting FasL-mediated counterattack against antitumor lymphocytes have been achieved exptl. in vitro, transferring such approaches to in **vivo therapy** represents an enormous challenge.
ST **review** Fas ligand cancer immunotherapy target
IT Antitumor agents
Apoptosis
Immunomodulators
Immunotherapy
(fas ligand as potential target for therapeutic induction of apoptosis and enhancing immunotherapy in cancer)
IT Fas antigen
Fas ligand
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(fas ligand as potential target for therapeutic induction of apoptosis and enhancing immunotherapy in cancer)
RE.CNT 98 THERE ARE 98 CITED REFERENCES AVAILABLE FO

ANSWER 22 OF 62 CAPLUS COPYRIGHT 2004 ACS on STN

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TI Fas ligand: a potential target for therapeutic induction of apoptosis and enhancing immunotherapy in cancer

AU O'Connell, Joe

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CODEN: ETTAF7; ISSN: 1460-0412

PB Ashley Publications

DT Journal; General Review

LA English

CC 1-0 (Pharmacology)
Section cross-reference(s): 15

AB A **review** with 98 refs. Fas (CD95/APO-1) is a cell surface receptor which mediates a potent apoptotic death signal upon engagement by its ligand, FasL. Since tumor cells frequently co-express Fas and FasL, the prospect of therapeutically stimulating autocrine suicide of cancer cells via the Fas pathway is tantalizing. To achieve this, mechanisms of acquired resistance to Fas-mediated apoptosis, inherent in cancers, must be overcome. Indeed, expression of FasL by Fas-resistant tumors appears to enhance malignancy by triggering apoptosis of Fas-sensitive antitumor immune effector cells. Therapeutic inhibition of this 'Fas counterattack' against antitumor immune responses might improve immunotherapeutic approaches. Although restoring the Fas-sensitivity of tumors and inhibiting FasL-mediated counterattack against antitumor lymphocytes have been achieved exptl. in vitro, transferring such approaches to in **vivo therapy** represents an enormous challenge.

ST **review** Fas ligand cancer immunotherapy target

IT Antitumor agents
Apoptosis
Immunomodulators
Immunotherapy
(fas ligand as potential target for therapeutic induction of apoptosis and enhancing immunotherapy in cancer)

IT Fas antigen
Fas ligand
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(fas ligand as potential target for therapeutic induction of apoptosis and enhancing immunotherapy in cancer)

RE.CNT 98 THERE ARE 98 CITED REFERENCES AVAILABLE FO

ANSWER 22 OF 62 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:3109 CAPLUS
DN 132:259965
ED Entered STN: 03 Jan 2000
TI Fas ligand: a potential target for therapeutic induction of apoptosis and enhancing immunotherapy in cancer
AU O'Connell, Joe
CS Department of Medicine, University Hospital, Cork, Ire.
SO Emerging Therapeutic Targets (1999), 3(4), 601-611
CODEN: ETTAF7; ISSN: 1460-0412
PB Ashley Publications
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
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ANSWER 21 OF 62 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 10

AN 2000:170406 CAPLUS

DN 132:263753

ED Entered STN: 16 Mar 2000

TI Genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents

AU Bodey, Bela; Bodey, Bela, Jr.; Siegel, Stuart E.; Kaiser, Hans E.

CS Department of Pathology, School of Medicine, University of Southern California, Los Angeles, CA, USA

SO Current Pharmaceutical Design (2000), 6(3), 261-276
CODEN: CPDEFP; ISSN: 1381-6128

PB Bentham Science Publishers

DT Journal; General Review

LA English

CC 15-0 (Immunochemistry)
Section cross-reference(s): 1

AB A **review** with 180 refs. Classical therapeutic modalities such as surgery, radiation, and chemotherapy not only fail to cure the great majority of malignant tumors, but their employment often leads to severe and debilitating side effects. The severe cancer related morbidity is also in direct correlation with the use of x-radiation and chemotherapy, making them less than ideal forms of therapy. The development of hybridoma technol. and the advances in monoclonal antibody (MoAB) production have revitalized the initial concept of Ehrlich concerning the existence of cancer cell-targeted, specific "magic bullets". Entirely new approaches to cancer therapy that are neoplastic cell-directed, and specifically lethal to malignant cells and less toxic to normal tissues are being observed and developed, adhering to the old prayer: "Destroy the diseased tissues, preserve the normal.". Immunotherapy as a fourth modality of cancer therapy has already been developed and proven to be quite effective. Strategies for the employment of antibodies for anti-cancer immunotherapy include: Immune reaction directed destruction of cancer cells; Interference with the growth and differentiation of malignant cells; Antigen epitope directed transport of anti-cancer agents to malignant cells; Anti-idiotype vaccines; and Development of engineered (humanized) mouse monoclonals for anti-cancer therapy. In addition, a variety of different agents (e.g. toxins, radionuclides, chemotherapeutic drugs) have been conjugated to mouse and human MoABs for selective delivery to cancer cells. Preclin. observations in athymic, nude mice using xenografted human cancers and mouse, anti-human MoABs were more than impressive and have lead to the development of clin. trials. Phase I studies established the safety of employing immunoconjugates in humans, but the in **vivo therapeutic** results were less impressive. The clin. use of mouse MoABs in humans is limited due to the development of a foreign anti-globulin immune response by the human host. Genetically engineered chimeric human-mouse MoABs have been developed by replacing the mouse Fc region with the human constant region. Moreover, the framework regions of variable domains of rodent Igs were also exptl. replaced by their human equivalent These antibodies can also be designed to have specificities and effector functions determined by researchers, which may not appear in nature. The development of antibodies with two binding ends (bispecific antibodies) provided a great improvement in targeting cancer cells. The existing inadequacies of MoABs in immunotherapy may also be improved by increasing their efficiency with chemical coupling to various agents such as bacterial or plant toxins, radionuclides or cytotoxic drugs. The astonishing immunophenotypic (IP) heterogeneity of neoplastically transformed cells, the different cytotoxic activity associated with the moiety linked to given MoABs, and mostly the impressive genetic modulation capabilities of cancer cells still remain as yet unsolved difficulties in the present immunotherapy of human cancer. In writing this **review** article, one of our main goals is to encourage further clin. research with the use of genetically engineered rodent MoABs

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and various immunoconjugates in the treatment of human cancer, as well as the combination of such immunotherapy with the three conventional modalities of therapy. Finally, we propose that MoAB-based immunotherapy be accepted as a conventional form of therapy and employed not only in terminal cancer patients but also, for instance, during and following surgical resection.

ST **review** immunotherapy chemotherapy anticancer monoclonal antibody

IT Drug targeting
(cancer cell specific; genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents)

IT Antitumor agents
Immunotherapy
(genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents)

IT Drug delivery systems
(immunoconjugates; genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents)

IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents)

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